FEATURE ARTICLES

Fluid Resuscitation for Hemorrhagic Shock in Tactical Combat Casualty Care
TCCC Guidelines Change 14-01 – 2 June 2014

Frank K. Butler, MD; John B. Holcomb, MD; Martin A. Schreiber, MD;
Russ S. Kotwal, MD; Donald A. Jenkins, MD; Howard R. Champion, MD, FACS, FRCS;
F. Bowling; Andrew P. Cap, MD; Joseph J. Dubose, MD; Warren C. Dorlac, MD;
Gina R. Dorlac, MD; Norman E. McSwain, MD, FACS; Jeffrey W. Timby, MD;
Lorne H. Blackbourne, MD; Zsolt T. Stockinger, MD; Geir Strandenes, MD;
Richard B, Weiskopf, MD; Kirby R. Gross, MD; Jeffrey A. Bailey, MD

ABSTRACT

This report reviews the recent literature on fluid resuscitation from hemorrhagic shock and considers the applicability of this evidence for use in resuscitation of combat casualties in the prehospital Tactical Combat Casualty Care (TCCC) environment. A number of changes to the TCCC Guidelines are incorporated: (1) dried plasma (DP) is added as an option when other blood components or whole blood are not available; (2) the wording is clarified to emphasize that Hextend is a less desirable option than whole blood, blood components, or DP and should be used only when these preferred options are not available; (3) the use of blood products in certain Tactical Field Care (TFC) settings where this option might be feasible (ships, mounted patrols) is discussed; (4) 1:1:1 damage control resuscitation (DCR) is preferred to 1:1 DCR when platelets are available as well as plasma and red cells; and (5) the 30-minute wait between increments of resuscitation fluid administered to achieve clinical improvement or target blood pressure (BP) has been eliminated. Also included is an order of precedence for resuscitation fluid options. Maintained as recommendations are an emphasis on hypotensive resuscitation in order to minimize (1) interference with the body's hemostatic response and (2) the risk of complications of overresuscitation. Hextend is retained as the preferred option over crystalloids when blood products are not available because of its smaller volume and the potential for long evacuations in the military setting.

KEYWORDS: *hemorrhage, fluid resuscitation, shock, plasma, blood products, damage control resuscitation*

Proximate Cause for This Proposed Change

Since the last update to the fluid resuscitation recommendations in the TCCC Guidelines in November 2011, there have been a number of publications related to hypotensive resuscitation, the use of DP, adverse effects resulting from the administration of both crystalloids and colloids, prehospital resuscitation with thawed plasma and red blood cells (RBCs), resuscitation from combined hemorrhagic shock and traumatic brain injury (TBI), balanced blood component therapy in DCR, the benefits of fresh whole blood (FWB) use, and resuscitation from hemorrhagic shock in animal models where the hemorrhage is definitively controlled prior to resuscitation.

Additionally, recently published studies describe an increased use of blood products by coalition forces in Afghanistan during Tactical Evacuation (TACEVAC) Care and even in TFC. Resuscitation with RBCs and plasma has been associated with improved survival on the platforms that use them, even in the relatively short evacuation times seen in Afghanistan in recent years.[1,2] Prehospital blood products may have an increasingly important impact on survival if evacuation times lengthen as the drawdown in Afghanistan continues and if the US military is called on to conduct operations in less mature theaters of conflict. Future conflicts in other geographic combatant commands such as the US Pacific Command (PACOM), the US Southern Command (SOUTHCOM), and the US Africa Command (AFRICOM) may have prolonged evacuation times and may include the need to consider preevacuation treatment aboard ships at sea.

This review presents the recent literature on fluid resuscitation and makes updated recommendations for

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the resuscitation of casualties who are in hemorrhagic shock during TCCC.

Background

New concepts in resuscitation from hemorrhagic shock (or renewed interest in older concepts) have been emerging in recent years. A report from 1993 noted that initial resuscitation for hemorrhagic shock in trauma patients was done almost exclusively with crystalloids.[3] A 2013 report on fluid resuscitation included a statement that minimization of crystalloids is a widely adopted practice in the resuscitation of patients suffering from hemorrhagic shock.[4] How did we make the journey between these two positions?

When the first TCCC report was being written, the recommended prehospital fluid resuscitation per the Advanced Trauma Life Support (ATLS) course was 2L of crystalloid (normal saline [NS] or lactated Ringer's solution [LR]).[5] The Ben Taub report published in 1994, however, found that large-volume crystalloid resuscitation for hypotensive patients with penetrating torso trauma prior to definitive surgical repair of the bleeding site produced a significantly lower survival rate compared with that obtained from delaying aggressive volume replacement until after surgical control of the bleeding.[6] Based on this study, with supporting data from multiple animal studies, the original TCCC recommendations regarding fluid resuscitation on the battlefield were:

1. Obtaining intravenous (IV) access and fluid resuscitation should be delayed until TFC;
2. No IV lines or IV fluids were recommended for casualties not in shock;
3. No IV fluids were recommended for casualties in shock resulting from uncontrolled hemorrhage;
4. 1000mL of Hespan was recommended as initial treatment for casualties in shock resulting from hemorrhage that has been controlled; and
5. The recommended maximum volume of Hespan was 1500mL.[7,8]

The expert panel that was convened by the US Special Operations Command in 1999 to discuss the US casualties in the battle of Mogadishu, however, recommended unanimously that casualties with a decreased state of consciousness resulting from hemorrhagic shock should be resuscitated with fluids immediately. The consensus approach was to restore some measure of perfusion without raising the BP sufficiently to disrupt a forming clot or create a dilutional coagulopathy.[9] This approach was echoed in a series of jointly sponsored US Army Medical Research and Materiel Command (MRMC) and Office of Naval Research (ONR) Fluid Resuscitation Conferences held in 2001 and 2002. These conferences were co-chaired by COL John Holcomb and Dr Howard Champion and produced the 2003 TCCC fluid resuscitation guidelines below[10,11]:

1. Assess for hemorrhagic shock; altered mental status (in the absence of head injury) and/or weak or absent peripheral pulses are the best field indicators of shock;
2. If the casualty is not in shock, then no IV fluids are indicated;
3. Oral (PO) fluids are permissible if the casualty is conscious and can swallow;
4. If in shock, administer a 500mL bolus of Hextend: Repeat once after 30 minutes if the casualty is still in shock. In general, do not give more than 1000mL of Hextend.

The fluid resuscitation guidelines just outlined are still in use by the US military. This approach to battlefield fluid resuscitation was revisited by an MRMC-sponsored conference on this topic held in January 2010. Sixty-five participants with expertise in fluid resuscitation were invited to present and to review the evidence in favor of or refuting the "hypotensive resuscitation with Hextend" strategy. A consensus document was produced and no change to this approach to battlefield fluid resuscitation was recommended.[12] Note that by this point in time, packed RBCs (PRBCs) had also been recommended for use if available in the TACEVAC phase of care.[13]

The most recent change to fluid resuscitation in TCCC was proposed by CAPT Jeff Timby and adopted by the Committee on Tactical Combat Casualty Care (CoTCCC) in 2011.[14] Additional elements added by this change included:

1. In TFC, if a casualty with altered mental status due to suspected TBI has a weak or absent peripheral pulse, resuscitate as necessary to maintain a palpable radial pulse.
2. The concept of 1:1 plasma and RBC resuscitation during the TACEVAC phase of care was incorporated. The use of FWB was also recommended as a secondary option if combat medical personnel are trained in this technique and an approved protocol is in place.
3. BP monitoring should be available in TACEVAC and should be used to guide resuscitation in this phase of care. The target systolic BP (SBP) is 80 to 90mmHg unless TBI is present, in which case the target SBP is 90mmHg or higher.
4. If blood products are not available in this phase of care and 1000mL of Hextend has been administered, continue resuscitation with Hextend or crystalloid solution as needed to maintain the target BP or to produce clinical improvement.

Discussion

Water comprises 60% of human body weight. Two-thirds of body water (40% of body weight) is intracellular and one-third of body water (20% of body weight) is extracellular. Of the extracellular water, three-quarters (15% of body weight) is interstitial and one-quarter (5% of body weight) is intravascular.[15]

There are a number of indications for IV fluid resuscitation, including sepsis, dehydration, burns, and hemorrhagic shock. This report will focus on fluid resuscitation from hemorrhagic shock. There are four objectives of prehospital fluid resuscitation for casualties in hemorrhagic shock:

1. Enhance the body's ability to form clots at sites of active bleeding with platelets, plasma, and RBCs;
2. Minimize adverse effects (edema and dilution of clotting factors) resulting from iatrogenic resuscitation injury;
3. Restore adequate intravascular volume and organ perfusion prior to definitive surgical hemorrhage control;
4. Optimize oxygen carrying capacity insofar as feasible.

This report will consider both the volume of fluid to be administered and the types of fluid that will be of most benefit in achieving these four objectives.

The goal of restoring intravascular volume is the only objective that can be met by all of the resuscitation fluid options that will be discussed. Restoration of oxygen-carrying capacity can be accomplished only with RBC units or whole blood. Platelets can only be replaced by transfusing platelets or whole blood. Coagulation factors can be replaced by transfusing whole blood or either liquid (never frozen) or thawed plasma, or reconstituted DP.

Resuscitation from hemorrhagic shock has historically been based on limited evidence. There was no strong evidence of equivalent efficacy before transfusion practice moved from whole blood to blood component therapy after the latter option became practical in the early 1970s. There is Level B evidence that large-volume crystalloid resuscitation in trauma patients with uncontrolled hemorrhage and shock increases mortality, yet this remains common practice. Blunt trauma patients may not benefit equally from fluid resuscitation strategies that are based on evidence from studies of penetrating trauma patients. Patients with shock from hemorrhage that has been controlled may not be best served by resuscitation strategies based on evidence obtained in studies of noncompressible hemorrhage. The presence of TBI in addition to hemorrhagic shock may also require modifications to fluid therapy in order to optimize outcomes, yet fluid resuscitation strategies often do not take any of these factors into account. Previous ATLS recommendations for initial fluid resuscitation of patients in shock called for a large volume (2L) of crystalloid, despite the dubious benefits of this intervention. The recommended initial crystalloid volume in ATLS is now 1L.[16] Infusion of large volumes of crystalloid may result in pulmonary edema, displacement of forming clots at sites of vascular injury, abdominal compartment syndrome, acidosis, worsening of cerebral edema, and dilutional coagulopathy.[17,18]

The applicability of even high-quality evidence to a particular clinical question is limited by the degree to which the characteristics of the patients to be treated match the inclusion criteria for the study cited. In order to understand fully the information obtained from fluid resuscitation studies in trauma patients and to know how best to apply that information, one must consider the type of hemorrhage that produced the shock state (controlled versus uncontrolled), the specific resuscitation fluids used, the severity of the shock that is being treated, the volume administered, the presence or absence of TBI, and the types and amounts of other fluids given in addition to the fluids that are the primary focus of the study. The need for caution in interpreting the results of resuscitation in trauma patients without considering the types of inclusion criteria noted here was highlighted recently by Dries.[19]

For example, the Ben Taub prospective, randomized trial on the early use of large-volume crystalloid resuscitation prior to surgical control of bleeding in hypotensive victims of penetrating thoracoabdominal trauma is the best evidence available for that subset of trauma patients.[6] If, however, the same question is asked for hypotensive victims of blunt or blast trauma, there is no assurance that the answer will be the same. The evidence produced by a study is applicable only to patients who both meet the inclusion criteria and are treated in similar circumstances. A caveat of the Ben Taub study is that the mean transport time was 15 minutes. That limits the applicability of the study's findings for casualties in military operations, where evacuation times may average 2 to 4 hours, as they did in Operation Desert Storm.[20] Much longer evacuation times have been seen in other combat actions, such as the Battle of Mogadishu (15 hours), early entry into Afghanistan and Iraq (4 to 6 hours), and recent military operations in Africa (4 hours).

Resuscitation Fluid Volume— Uncontrolled Hemorrhage

The optimal volume of resuscitation fluid is not necessarily the same for those patients with controlled hemorrhage and those with uncontrolled hemorrhage. In controlled hemorrhage (e.g., casualties with isolated

extremity or junctional injury in which bleeding has now been controlled with an extremity or junctional tourniquet), the hemorrhage has been effectively controlled and restoration of a normal or near-normal BP would be less likely to exacerbate any ongoing hemorrhage. That said, casualties who have tourniquets applied should be continuously reassessed during and after fluid resuscitation to see if the fluid administered has resulted in recurrent bleeding from the injured extremity or junctional area.

In uncontrolled hemorrhage (e.g., casualties with penetrating injury to the chest, abdomen, or pelvis), bleeding occurs at an internal site not visible to combat medical personnel and not amenable to prehospital hemorrhage control interventions. The entry site may be inconspicuous and obscured by the casualty's uniform. The combination of decreased blood flow to the bleeding site and the body's clotting response may result in an initial cessation of blood loss, but this cessation may be temporary if BP is subsequently raised and resuscitation fluids that do not contain platelets or clotting factors are used. Both crystalloids and colloids dilute the concentration of clotting factors in the intravascular space. The combined increase in BP and dilutional coagulopathy may overwhelm the body's attempts to achieve hemostasis at the site of vascular injury.

Sondeen and colleagues studied the BP at which animals with a standardized intra-abdominal injury (aortotomy) resuscitated with LR began to rebleed. The average BP at which rebleeding occurred was a mean arterial pressure (MAP) of 64 ± 2mmHg (SBP 94 ± 3mmHg).[21] The authors recommended that resuscitation of patients with uncontrolled hemorrhage be accomplished to an end point that would result in a BP below this level.

For uncontrolled (noncompressible) hemorrhage, there is Level B evidence that early, aggressive crystalloid resuscitation prior to surgical control of bleeding results in decreased survival compared with fluid resuscitation that is delayed until after surgical hemostasis.[6] This was a prospective, randomized, controlled trial in which 598 hypotensive patients with penetrating torso trauma were resuscitated either aggressively with Ringer's acetate (mean 2478mL) or with only a minimal fluid volume (mean 375mL) prior to surgery.[6] Survival was 70% in the 289 patients who received the restricted volume presurgical fluid resuscitation and 62% in the 309 patients who received the aggressive, larger-volume early fluid resuscitation ($p = .04$). These findings are consistent with the observations made by Beecher in World War II[22] and Cannon and colleagues in World War I.[23]

More recent clinical studies also support this finding.[24,25] Duke's retrospective study of 307 patients with penetrating torso injuries and hypotension found that those who received standard fluid resuscitation (defined in that study as greater than 150mL of crystalloid, with a mean volume infused of 2757mL) had a higher intraoperative mortality (32%) than those whose fluid resuscitation was restricted to 150mL or less (mean 129mL). The intraoperative mortality was 9% in the restricted fluid resuscitation group ($p < .001$).[24] In another study on the effect of infused crystalloid volume on mortality, volumes of 1.5L or more in the emergency department were associated with increased mortality. The patients in this study were not categorized by mechanism of injury or by controlled versus uncontrolled hemorrhage.[25]

Hampton and colleagues prospectively studied 1200 trauma patients (65% blunt trauma; 35% penetrating) as part of the PRospective Observational Multicenter Massive Transfusion (PROMMTT) study; 84% of patients received prehospital IV fluids, while 16% did not. The patients in this study were not grouped by controlled versus uncontrolled hemorrhage. Injury Severity Scores (ISSs) were similar. The median volume of fluid infused was 700mL. The authors found that prehospital IV fluid administration was not associated with an increase in SBP but was associated with increased survival (hazard ratio 0.84, 95% confidence interval 0.72 to 0.98; $p = .03$).[26]

In an analysis of a prospectively collected multicenter cohort of severely injured blunt trauma patients who were in hemorrhagic shock, the amount of crystalloid given was directly associated with the incidence of abdominal compartment syndrome (ACS), extremity compartment syndrome, adult respiratory distress syndrome (ARDS), multiple organ failure, and infections. There was no observed effect on in-hospital mortality.[27] In a retrospective study of 799 patients at a Level 1 trauma center, Joseph and colleagues found that the volume of crystalloid resuscitation was the only risk factor associated with the development of ACS.[28]

A retrospective study based on data from the Trauma Registry of the German Society for Trauma Surgery compared 1351 pairs of patients with an ISS greater than 16 who were given relatively less (0 to 1500mL) or relatively more (2000mL or more) prehospital crystalloids or colloids.[29] This study found that those who received the larger-volume prehospital fluid resuscitation received significantly more units of PRBCs (9.2 versus 6.9 units) and had significantly increased trauma-associated coagulopathy (72% versus 61.4%) and increased rates of sepsis (18.6% versus 13.8%) and organ failure (39.2% versus 36.0%). In another study from Tulane examining the effect of plasma-to-RBC ratio in massive transfusion patients, increasing volume of crystalloid administration during the resuscitation was

found to cause increased morbidity (bacteremia, ARDS, and renal failure).[4]

In a swine model of uncontrolled hemorrhage using a Grade V liver injury, Riha and colleagues found that the "no fluid" resuscitation option resulted in the least postresuscitation bleeding.[30] Other resuscitation fluids used in this study were LR, Hextend, hypertonic saline (HTS), and NS. Although not statistically significant, all animals in each arm of the study (n = 10) survived for the 120-minute study period except for two animals in the no-fluid arm.[30]

In the combat setting, the unwarranted use of large-volume crystalloid has another negative impact. In the past, combat medical personnel often carried 10 to 20 pounds of LR or NS in their combat medical packs. This extra carriage weight has an unquantified but undoubtedly detrimental effect on their combat effectiveness. In addition, time was wasted and lives were placed at risk on the battlefield in order to perform an intervention of dubious benefit.

Restricted fluid resuscitation is now used in many civilian trauma systems.[19,31–33] The Eastern Association for the Surgery of Trauma 2009 Practice Management Guidelines states that: "There is insufficient data to suggest that blunt or penetrating trauma patients benefit from prehospital fluid resuscitation. In patients with penetrating injuries and short transport times (less than 30 minutes), fluids should be withheld in the prehospital setting in patients who are alert or have a palpable radial pulse. Fluids (in the form of small boluses, ie, 250mL) should be given to return the patient to a coherent mental status or palpable radial pulse. In the setting of traumatic brain injury, however, fluids should be titrated to maintain SBP greater than 90mm Hg (or MAP greater than 60mmHg). HTS boluses of 250mL seem equivalent in efficacy to 1000mL boluses of standard solutions (LR, 0.9% sodium chloride). There is insufficient evidence to show that injured patients with short transport times benefit from prehospital blood transfusions. Finally, rapid infusion systems and or pressurized devices (to deliver fluids more rapidly) should not be used in the prehospital setting."[33]

Beecher noted during World War II that, even when blood products are being used, there was no need to raise the SBP above 80mmHg.[22] Strandenes and colleagues note that hypotensive resuscitation is the standard in resuscitating casualty from hemorrhagic shock.[34]

For medics on the battlefield who typically do not have access to BP monitors, improvement in level of consciousness and the presence of a radial pulse have been used as surrogate markers for BP. Although some authors have disputed the 1985 ATLS teaching (now discontinued) that the presence of a radial pulse indicates a BP of 80 or higher,[35,36] the larger study of 342 trauma patients performed by McManus and colleagues found that a radial pulse character described as "weak" (mean SBP of 99.9mmHg) by prehospital providers was 26mmHg lower than a pulse described as "normal" (mean SBP of 128.7mmHg).[37]

Based on the above, for casualties with suspected uncontrolled hemorrhage and no TBI, the target SBP should be 80 to 90mmHg. If BP monitoring is not available, either improved level of consciousness or a weakly palpable radial pulse may be used as a surrogate marker for SBP. Future advances in prehospital monitoring capabilities may enable battlefield trauma care personnel to more precisely judge the adequacy of fluid resuscitation using such technologies as tissue oxygen saturation[38] or the cardiovascular reserve index.[39]

Resuscitation Volume—TBI

The TCCC Guidelines call for a modified fluid resuscitation regimen for casualties suffering from both hemorrhagic shock and TBI.[13,14,40] In these casualties, decreased level of consciousness may result from either the TBI or hemorrhagic shock. Hypotension in the presence of TBI is associated with increased mortality.[41]

Because of the need to maintain an adequate cerebral perfusion pressure, casualties with TBI should be resuscitated to an SBP of 90mmHg or greater even in the presence of possible uncontrolled hemorrhage. If BP monitoring is not available, resuscitate as needed to maintain a normal radial pulse, since altered mental status in these casualties may be due to the TBI.[13,14]

Resuscitation Fluid Volume—Controlled Hemorrhage

Kragh et al.'s 2009 study on prehospital tourniquet use found that casualties with tourniquets applied before the onset of shock had a survival rate of 94%, while casualties who had tourniquets applied after shock was already present had a survival rate of 17%.[42] This study did not describe what fluid resuscitation strategy, if any, was used for these casualties.

No prospective, randomized trials that focused specifically on prehospital fluid resuscitation for trauma patients in shock from hemorrhage that had been controlled were found, but there have been animal models that address this question. In a recent study of fluid resuscitation in a swine model of uncontrolled hemorrhage, the animals were bled 60% of their total blood volume—with a femur fracture superimposed on the

hemorrhage—and were resuscitated with Hextend or LR. Shed blood was replaced with an equal volume of Hextend. (Note that, in a human, a 60% loss of blood volume would equate to 3L; 3L of Hextend would be a much larger resuscitation volume than the currently recommended 500mL with one repeat dose as needed.) All 14 study animals survived the 6-hour study period. The 6-hour observation period in this report is relevant to military operations, in which prolonged evacuation times may not be the norm, but are always a possibility. Six hours may not, however, be long enough to observe some potential complications of fluid resuscitation such as ARDS, extremity compartment syndrome or ACS, or acute kidney injury. The animals resuscitated with LR also all survived but required 118 ± 3mL/kg of fluid for resuscitation—almost 3 times as much fluid—to maintain their hemodynamic status as did the Hextend animals (42mL/kg), reinforcing the point that Hextend achieves equal volume expansion with much less equipment weight for combat medics, corpsmen, and pararescuemen (PJs). In addition, the mean lactate levels in the LR group at the end of the 6-hour period were twice that of the Hextend group, indicating that resuscitation was more effective with Hextend, although the lactate infused with the LR might also contribute to the increased lactate level. The Hextend animals were more coagulopathic than the LR animals, but that did not result in decreased survival in this controlled hemorrhage model.[43] The relevance of this model to combat casualties must be tempered with the understanding that the polytrauma often seen on the battlefield makes it difficult to establish with certainty that noncompressible hemorrhage is not also present.

In another study by Burns and colleagues, male miniature swine were hemorrhaged 60% of their estimated blood volume and then resuscitated with 1mL/kg/min of Hextend to an SBP of either 65mmHg or 80mmHg. The animals were then observed for 180 minutes. The mean survival time for the control (unresuscitated) animals was 64 minutes; the survival rate in this group at 180 minutes was 6%. Survival at 180 minutes was 86% for the animals resuscitated to 65mmHg and 100% for those resuscitated to 80mmHg.[44] The mean replacement volume of Hextend needed to maintain an SBP of 65mmHg was 265mL; for 80mmHg, the required volume was 640mL. (The shed blood volume in this swine model was approximately 1700mL.) Replacing a 3000mL blood loss volume for volume in a human would mean infusing 3L of Hextend, while the equivalent volumes suggested by the Burns et al. study to achieve the lower SBPs of 65mmHg and 80mmHg would be 467mL and 1129mL, respectively.

The Burns et al. study suggests that resuscitating a casualty with hemorrhagic shock to an SBP of 80mmHg should produce 100% survival if his or her hemorrhage has been effectively controlled and that the Hextend volume currently recommended should be sufficient to achieve this target SBP. The authors found no clinical studies that confirm this, but a recent unpublished case report described a casualty with an isolated extremity wound. Tourniquet placement was delayed due to an ongoing firefight and the casualty became unconscious from hemorrhagic shock. The treating medic subsequently placed a tourniquet to control the bleeding and then administered 500mL of Hextend. The casualty regained consciousness and had a Glasgow Coma Scale score of 15 by the time he was evacuated. There was no evidence of acute kidney injury during his subsequent stays at several hospitals in the continuum of care.[45]

Casualties with isolated hemorrhage that has been controlled with certainty (ie, shock due to an isolated extremity gunshot wound now controlled with a tourniquet) can be resuscitated to a higher BP (greater than 90mmHg).

However, on the battlefield, the number of casualties with hemorrhagic shock in whom ongoing uncontrolled hemorrhage can be definitively ruled out is limited. Thus, in casualties with penetrating torso trauma, blunt trauma, or blast trauma who may still have noncompressible hemorrhage, once external hemorrhage is adequately controlled, they should still have a target SBP of 80 to 90mmHg. A weakly palpable radial pulse or improved level of consciousness may be used as end points for resuscitation if BP monitoring is not available. This will provide adequate resuscitation for these casualties while reducing the risk of dilutional coagulopathy and disturbing clot formation at noncompressible bleeding sites.

Prehospital Resuscitation Fluid Options

Early in the conflicts in Afghanistan and Iraq, military trauma surgeons observed that the large-volume crystalloid resuscitation and low volumes of plasma used for initial in-hospital resuscitation might be exacerbating the coagulopathy of trauma and causing excess deaths from uncontrolled hemorrhage.[46–48] The principles of DCR emphasize a balanced transfusion strategy in which plasma (with its clotting factors) was transfused in an equal ratio to the number of RBC units administered. The use of crystalloids during resuscitation was minimized. DCR is now the standard of care in deployed medical facilities.[38,47,49] Platelets have been shown to improve outcomes when available.[50]

Prehospital fluid resuscitation options are typically more limited based on the logistics of blood component available on the battlefield and the training level of combat

medical personnel, but the principles of DCR apply to this phase of care as well insofar as DCR is achievable in the far-forward environment. The fluid options for prehospital resuscitation from hemorrhagic shock are discussed next.

DCR With Whole Blood

Whole blood replaces coagulation factors and platelets, reverses intravascular volume deficit, and restores oxygen-carrying capability. It is noteworthy that, with the advent of the capability to fractionate whole blood into components, there was very limited evidence (especially in trauma patients) that component therapy was equivalent to whole blood transfusion in the treatment of hemorrhagic shock in trauma patients.[51–53] As non–whole blood transfusion regimens began to come into use and crystalloid was used with more frequency as part of the resuscitation, the complications of trauma-associated coagulopathy, ARDS, and ACS became more frequent.[53] Although 1:1:1 plasma:RBC:platelet component therapy is an attempt to approximate whole blood, these components as used in 1:1:1 resuscitation are anemic, coagulopathic, and thrombocytopenic in comparison to whole blood.[54,55] Elmer and colleagues note that 1:1:1 component therapy yields a combined transfusion product with an approximate hematocrit of 29%, a platelet count of 85,000/µL, and approximately 60% of normal clotting activity.[56] Any crystalloid or colloid used in the resuscitation further increases the severity of the iatrogenic coagulopathy through hemodilution.

In a retrospective study of 488 casualties, improved survival was noted when FWB was used in addition to PRBCs and plasma (common practice when platelets were not available), compared with the administration of RBCs and FFP without platelets or FWB.[57] In a retrospective study of 354 combat casualties, Spinella and coauthors found that 100 casualties treated with RBCs, plasma, and warm FWB (but not apheresis platelets) had a higher 30-day survival rate (95% versus 82%) than did 254 casualties treated with RBCs, plasma, and apheresis platelets (but not FWB).[58] Cold storage may extend the maximum storage period for whole blood, prompting a call for prospective trials of resuscitation with whole blood compared with component therapy.[51] One study of 591 massively transfused combat casualties found an association between warm fresh whole blood transfusion and a higher incidence of acute lung injury, but it was noted that warm FWB was administered preferentially to more severely injured patients, thus raising the possibility that the severity of the wounds rather than the FWB was responsible for the higher incidence of lung injury.[58]

A single-center randomized trial in a civilian setting found modified whole blood (non–platelet-sparing leukoreduction followed by the addition of apheresis platelets) was associated with 30-day survival that was similar to 1:1:1 component therapy in 107 patients.[53] A review of 1745 patients with major trauma (age 18 to 45 years, ISS greater than 25, and received blood transfusions) from the 2009 National Trauma Data Bank found that patients who were treated with blood component therapy were 3.2 times more likely to die than were those treated with whole blood ($p = .010$).[59]

Although FWB collected in emergent circumstances in the theater is not screened to the same extent as would be the case in routine blood banking practice and therefore is not US Food and Drug Administration (FDA) compliant, the Assistant Secretary of Defense For Health Affairs has recognized the possible need to use noncompliant blood products in deployed medical settings and defined the procedures that must be followed to address typing considerations and infection surveillance for noncompliant blood products.[60] The Joint Trauma System Clinical Practice Guideline (CPG) on FWB states that FWB is indicated only when ". . . other blood products are unable to be delivered at an acceptable rate to sustain the resuscitation of an actively bleeding patient, when specific stored components are not available (e.g., RBCs, platelets, cryo, thawed plasma), or when stored components are not adequately resuscitating a patient with an immediately life-threatening injury."[61] The JTTS Damage Control CPG notes that FWB is "at least equivalent to component therapy and at best is independently associated with improved survival."[49] This guidance is further supported by the findings of Perkins and coauthors who compared the transfusion of platelets as either FWB or apheresis platelets in massive transfusion combat trauma patients and found similar outcomes.[62]

Noting that crystalloids and colloids add weight and bulk to the medic's kit and that their use may result in resuscitation injury (including acidosis, hypothermia, ARDS, ACS, and dilutional coagulopathy), Strandenes and his colleagues and others have called for increased emphasis on far-forward blood transfusion programs.[63–66] Far-forward FWB transfusions have been successfully carried out during the conflicts in Iraq and Afghanistan, and protocols have been developed to enable this intervention to be safely used by advanced capability providers trained to perform it.[64,65,67] Far-forward blood is hardly a new concept—there is a case report of its successful use to treat a British casualty in shock in the trenches during World War I.[68] New cold storage and pathogen reduction techniques may also enable whole blood to be safely stored for longer periods and thus increase its availability for use in farther forward treatment locations.[50] An effective general pathogen reduction system would reduce the screening requirements currently used to prevent transfusion-transmitted diseases and protect blood supplies against emerging and nonviral pathogens.[69] Hooper

and his colleagues note that much of the resistance to the use of far-forward fresh whole blood is the perceived risk associated with its use but that this risk may be less than that associated with other life-saving interventions undertaken in the prehospital combat environment, such as surgical airways and endotracheal intubation.[38]

DCR With 1:1:1 Component Therapy

Brohi and colleagues documented that trauma-related coagulopathy was present in 25% of severely injured blunt trauma patients brought to a large trauma center, even before significant fluid resuscitation.[70] Coagulopathy has been documented in 38% of combat casualties who require transfusion.[71] Trauma-related coagulopathy is associated with a 3- to 6-fold increase in mortality.[71,72] A recent review of 3632 casualties in the Department of Defense Trauma Registry (DoDTR) who received at least one blood product found that there was a 33% incidence of coagulopathy (INR greater than or equal to 1.5) and that coagulopathy was associated with a 5-fold increase in mortality.[73]

Both the prehospital resuscitation strategy recommended by ATLS at the onset of the Afghanistan conflict (2L of crystalloid) and the transfusion practices of many trauma centers at that time (which emphasized RBC administration with relatively fewer units of plasma and platelets) exacerbated the endogenous component of trauma-related coagulopathy by superimposing a dilutional coagulopthy.[46] Some civilian trauma centers began to administer RBCs, plasma, and platelets in a 1:1:1 ratio to decrease iatrogenic coagulopathy.[46,74–76]

A retrospective study of 694 massively transfused combat casualties treated at the military hospital in Baghdad found that patients receiving a higher ratio of platelets to RBCs had a 24-hour survival rate of 95% compared with a survival rate of 87% in patients with a medium platelet-to-RBC ratio and 64% for those with the lowest platelet-to-RBC ratio.[62] Cap and coauthors performed a retrospective analysis of 414 combat casualties from Iraq who received massive transfusions (defined as 10 or more units of RBCs within 24 hours). This study found that resuscitation with higher ratios of plasma and platelets to RBCs within the first 6 hours was associated with improved 24-hour and 30-day survival in combat casualties.[77] When platelets are not available, a plasma-to-RBC ratio of 1:1.5 or greater is also associated with improved survival.[48,78]

DCR using 1:1:1 plasma, RBCs, and platelets is now the standard of care for the US military for casualties requiring resuscitation from hemorrhagic shock.[49,79,80] DCR is also being used with increasing frequency in civilian trauma centers.[52,81,82] One study that questioned the use of the term "hemostatic resuscitation" to refer to DCR as well as the value of the DCR approach used

rotational thromboelastometry (ROTEM) measurements rather than mortality as an outcome measure and included trauma patients who did not receive massive transfusions in the analysis.[83]

As with whole blood collected in theater, the platelets used for 1:1:1 resuscitation in the US Central Command (CENTCOM) are also not FDA approved. An FDA-approved blood product must be collected at a blood bank that has a Biologic License Application with the FDA, fully certifying its standard operating procedures and quality control in accordance with FDA standards. All DoD blood centers in the continental United States meet these standards. Combat theater blood banking practice approximates these standards insofar as possible but deviates in two important ways: (1) Retrospective transfusion-transmitted disease (TTD) testing is conducted on each unit of product collected, but this is not done prospectively, so each unit is not virally "cleared" prior to release to the patient; and (2) platelets are kept up to 7 days if cultures are negative. Mitigation measures include tracking of recipients and matching with retrospective results to ensure proper care in the event of disease transmission; use of pedigreed donors (tested every 90 days) to minimize risk; and use of rapid tests prior to release of products for transfusion (note that these rapid tests are meant for screening, not blood donor qualification: a positive result helps, but a negative result does not guarantee product safety).[84] Thus, there is currently no way to administer either the best option (whole blood) or the second-best option (1:1:1 component therapy) in Afghanistan using FDA-compliant blood products.

DCR With 1:1 Component Therapy

DCR with a 1:1 ratio of plasma to RBCs is the highest level of hemostatic resuscitation that can be accomplished in theater using FDA-compliant blood products. The major challenge to achieving full FDA compliance is the inability to certify the TTD status of WB or apheresis platelets prior to transfusion. This is one of the major drivers for the DoD's WB pathogen reduction technology program.[84]

DCR using higher ratios of plasma to RBCs has now been shown to improve survival in massively transfused patients in both the military and civilian sectors.[48,52,73–75,78,85–89] Increasing the plasma-to-RBC ratio has a greater impact on outcomes for those casualties who receive massive transfusions (more than 10 units of RBCs in the first 24 hours) compared with those who receive smaller amounts of blood products.[90] Further, plasma has been shown to be of greater benefit when administered early in resuscitation.[91] It should be noted that the definition of massive transfusion is currently evolving from the 10 or more units of RBCs in

the first 24 hours used in many of the above studies to 3 or more units of RBCs in 1 hour.[92,93] In a study of 294 severely injured patients performed at Memorial Hermann Hospital in Houston, storing thawed plasma in the emergency department reduced the time delay to the first administration of plasma from 89 minutes to 43 minutes. This in turn was associated with a decrease in overall blood product use and a 60% odds reduction in 30-day mortality after controlling for admission injury severity and physiologic status.[94]

Another way to increase the availability of plasma for use earlier in the resuscitation of patients in hemorrhagic shock is to use liquid plasma (never-frozen) rather than FFP. Never-frozen liquid plasma has a favorable hemostatic profile compared with thawed plasma and can be stored at 1° to 6°C for up to 26 days.[95] This product is now being used on the helicopter service at Memorial Hermann Hospital in Houston because of its substantial logistical advantage.[96]

Prehospital resuscitation with balanced 1:1 RBC:plasma ratios is now being used in the civilian sector in the United States.[52,97] It has also been used successfully on the United Kingdom's Medical Emergency Response Team (MERT) evacuation platform in Afghanistan and may be a factor in the improved survival noted in the subset of severely injured casualties evacuated by the MERT compared with other evacuation platforms.[1,2] Plasma and RBCs should be available whenever logistically feasible on TACEVAC platforms[98] and may be available in some instances prior to TACEVAC, such as in mounted patrols[99] and on ships at sea. Prehospital resuscitation with RBCs and plasma in a civilian trauma system has been shown to improve acid-base status and to reduce early mortality in the sickest patients compared to resuscitation with crystalloids.[63]

Damage Control Resuscitation With RBCs
Brown and colleagues performed a retrospective study of 1415 severely injured blunt trauma patients, 50 of whom received RBCz before arrival at the trauma center. Pretrauma center administration of RBCs (median 1.3 units) was associated with a significant reduction in both 24-hour and 30-day mortality despite these patients being more severely injured and having a longer transport time than the patients who did not receive pretrauma center RBCs.[100] Sixty-one casualties transported on board US Army DUSTOFF evacuation helicopters were transfused with RBCs without any known adverse reactions or blood product wastage.[101]

DCR With Thawed Plasma or Liquid Plasma
Transfusion of plasma is the standard of care for the treatment of the coagulopathy of trauma, which is seen in a significant percentage of severely injured combat casualties.[32,71,102–105] In a case series from the Mayo Clinic, prehospital plasma administration has been shown to result in improved INRs by the time of arrival at the emergency department.[106] Additionally, plasma has much better buffering capacity than crystalloids and colloids[107] and has been shown in a large animal model of multisystem trauma to reduce platelet dysfunction in comparison to resuscitation with NS.[108]

In a swine model of resuscitation from uncontrolled hemorrhage with LR, Hextend, FFP, FFP and RBCs, and FWB, resuscitation with FFP produced the lowest postresuscitation blood loss of any of the fluids studied.[109] Blood loss using plasma as a resuscitation fluid was approximately half that seen in the Hextend animals. In another animal study that used a fixed-volume model of otherwise lethal hemorrhage in swine, resuscitation with type-compatible FFP was observed to produce a survival rate equal to resuscitation with whole blood and better than that seen with either albumin or NS.[110]

Mitra et al. showed that the administration of plasma in high ratio to PRBCs (greater than or equal to 1:2) versus a low ratio (less than 1:2) within 4 hours of presentation to the emergency department significantly improved survival ($p = .03$) in 159 trauma patients requiring a massive transfusion when a coagulopathy was present. No benefit was found in 179 patients in whom coagulopathy was absent.[111]

While there is no Level 1 evidence that documents improved survival from prehospital resuscitation with plasma alone, the available evidence indicates that this practice may improve outcomes for casualties with severe hemorrhage.[112]

DCR With DP
Although thawed plasma or liquid plasma is now being carried on some advanced capability TACEVAC platforms, these options are typically not available during TFC. Lyophilized (dried) plasma is a logistically attractive option for battlefield trauma care prior to TACEVAC.[32,52,98] DP offers the opportunity for both volume replacement and replacement of lost clotting factors. DP has been noted to have a good safety record[102,113] and has been approved for use by multiple coalition partner nations (United Kingdom, France, Germany, the Netherlands) in the Afghanistan conflict. The French lyophilized plasma product (FLyP) is now being used by some US Special Operations Forces under a treatment protocol, but the administrative aspects of the protocol are complex and time-consuming. Additionally, the cost per unit for FLyP is currently much higher than Hextend or crystalloids.[114] Another disadvantage of FLyP is the glass bottle in which the product is supplied, which is breakable and suboptimal for the medic's combat load.

FLyP is a "universal" product that can be used for casualties of any blood type. It is made by pooling A, AB, and B plasma from at least 10 donors.[112] The French hemovigilance system monitors adverse effects of blood component therapy, including FLyP; this system has reported no transmission of viral infections from the use of FLyP since it started tracking the use of this product in 1994.[115] To date, more than 1000 units have been administered with no documented adverse effects resulting from this product.[102,116] Martinaud et al. reported that 87 casualties received the French DP product at a Role 3 facility in Kabul from February 2010 to February 2011. These 87 casualties (70% of whom were Afghan) received a mean of 3.5 units of DP per transfusion episode without major adverse events.[113] In the published commentary that accompanied this report, Schreiber remarked that these results should be interpreted with caution because of missing data and the reported 10% mortality in this case series, but noted that the report is an important addition to the literature in that it is the first large-scale report of DP use in an injured patient cohort.

The German DP product (LyoPlas) is a quarantined, single-donor product. When stored at room temperatures for 24 months, the individual coagulation factors retain 75% to 100% of their activity. LyoPlas also enables rapid treatment of coagulopathies without the need for complex logistics or thawing. Over 230,000 units have been transfused to date with no reports of major adverse complications to include viral transmission. The frequency of transfusion reactions approximates that of FFP.[117] LyoPlas is type specific; type AB can be used if the recipient's blood type is unknown.[103] The Israeli Defense Force (IDF) has implemented a program to provide DP at the point of injury. The IDF program selected the German LyoPlas product, and it has now been used at the point of injury.[102]

No studies were found in this review that demonstrate a survival advantage from using plasma in the absence of RBCs in the prehospital environment. However, hemorrhage is the leading cause of preventable deaths in combat casualties.[118] When severe tissue injury is combined with systemic hypoperfusion, an endogenous coagulopathy ensues quickly.[119] Trauma-related coagulopathy is associated with a 3- to 6-fold increase in mortality.[71,72] Coagulopathy has been documented in 38% of combat casualties who require transfusion.[71] Trauma-associated coagulopathy has also been found to be common in studies of trauma patients with a predominantly blunt mechanism of injury and is associated with an increase in early deaths.[120] Plasma is the standard of care for treating the coagulopathy of trauma, while the use of crystalloids, colloids, or RBCs alone superimposes a dilutional coagulopathy to the endogenous coagulopathy of trauma. The prehospital administration of 2 units of thawed plasma

to nine hypotensive, tachycardic patients resulted in an improvement in INR from 2.6 at baseline to 1.6 on arrival at the ED.[106] In summary, combat casualties often have a coagulopathy; coagulopathy increases mortality, and plasma administration reduces the coagulopathy.

Lyophilized plasma has been found to be as effective as thawed plasma in a swine model of hemorrhagic shock and TBI. Both plasma products reduced the brain lesion size and cerebral edema compared with resuscitation with NS.[121,122] Preliminary animal models have also suggested that reconstituting DP with less diluent to create a hyperosmolar product may confer logistical and physiological benefits.[123]

There is increasing recognition of the need to provide resuscitation that both replaces plasma factors that help to reestablish homeostatic conditions (as neither crystalloids nor colloids do) and does not cause a fluid overload for patients prior to surgical control of bleeding. Hypotensive resuscitation with DP is the resuscitation option that holds the most promise for use in prehospital settings for casualties in shock when whole blood, RBCs, and thawed or liquid plasma are not available. This option is, however, not yet available to most US combat medics in the absence of an FDA-approved DP product.[103] Currently, the German LyoPlas product is being used by Germany, the Netherlands, the United Kingdom, Norway, Sweden, and Israel. The French FLyP product is being used by the French and by selected US military units.[112] Studies examining the impact of prehospital resuscitation with plasma compared with colloids and crystalloids are needed. These studies should also examine the impact of prehospital plasma resuscitation on surrogate outcome measures such as markers for coagulopathy and shock that could be more readily explored in smaller studies. European manufacturers of DP products are reluctant to undertake the expensive studies needed to allow them to enter the US market,[124] emphasizing the need for US manufactured and FDA-approved DP product. One means to expedite this would be the establishment of a military use panel within the FDA to study medications and blood products of unique value to the military and to consider them using methodology that recognizes the circumstances unique to the treatment of casualties in a deployed combat setting. Such a panel might also provide a military USP approval for FLyP and/or LyoPlas.

Blood Component Resuscitation Protocols
The success of in-hospital blood product administration in improving the survival of trauma patients is unquestioned, and blood product transfusions are the standard of care in both military and civilian trauma care. Use of blood products is an advanced lifesaving intervention that, until recently, was thought to be beyond the

capabilities of most prehospital trauma systems and providers. The prehospital administration of whole blood and/or blood components has now been proven feasible but requires meticulous attention to detail to accomplish safely.

In order to administer whole blood or blood component therapy safely and effectively, a command- or theater-approved protocol that has been coordinated with the appropriate blood banking facilities should be used. All medical personnel who will be responsible for administering blood products in the prehospital combat setting should be trained in the approved protocol.

The details of the protocol may vary depending on the maturity of the theater, service guidelines, the specific tactical scenarios envisioned, and the blood-banking logistics in the area of operations. In general, the following items should be addressed:

- Training of combat medical personnel in the approved protocol
- Documentation of this training
- Maintenance training interval
- Which blood products will be used (RBCs, FFP, etc.)
- Ratio of plasma and platelets to RBC units infused
- ABO and Rh compatibility issues
- Screening of potential donors
- Transport container to be used
- Transport container handling instructions
- Storage temperature requirements
- Storage temperature documentation requirements
- Disposition of unused units on return of containers
- Maximum time allowed for transport in a container
- Number and types of units to be transported
- Indications for transfusion
- Procedure for transfusion
- Equipment required
- Pretransfusion check of units
- Protective equipment required
- Transfusion rate
- Transfusion pressure
- Warming of units
- Walking blood bank procedures for fresh whole blood
- Prescreening for walking blood bank donors
- Postdonation procedures
- Minimum time between blood donations
- Monitoring during transfusion
- End points of resuscitation
- Management of transfusion reactions
- Documentation of transfusion[13]

Protocols have been developed for use by Special Operations units to help facilitate the use of whole blood in the far-forward combat environment. Strandenes and his colleagues note that the most critical skill required of combat medics in order to execute this protocol safely in the is the ability to reliably identify casualties who will benefit from whole blood transfusion.[63]

Crystalloids and Colloids—General
The best crystalloid or colloid fluid for resuscitation from hemorrhagic shock when blood products are not available is a topic of controversy.[15,30] Large volumes of crystalloid or colloid fluid administered in the prehospital setting are associated with worsening of the coagulation profile on arrival at the emergency department.[29] Resuscitation with large volumes of either crystalloids or colloids contributes substantially to trauma-associated coagulopathy.[32] The presence of a coagulopathy was found to nearly double the mortality in patients with traumatic subdural hematoma.[125]

The CRISTAL multicenter, randomized clinical trial compared resuscitation with colloids versus crystalloids in 2857 consecutive intensive care unit patients with shock from sepsis, trauma, or other causes. Worthy of note is that trauma patients comprised only 1.6% of the colloid group and 2.5% of the crystalloid group. The choice and volumes of crystalloid or colloid was based on the standard practice at each of the 57 participating hospitals. Crystalloids included isotonic saline or HTS and any buffered solutions. Colloids included both hypo-oncotic (e.g., gelatins, 4% or 5% albumin) and hyper-oncotic (e.g., dextrans, hydroxyethyl starches [HESs], and 20% or 25% albumin). The dose of HES used could not exceed 30 mL per kg of body weight per day. There was no difference in mortality at 28 days, but patients treated with colloids had improved survival at 90 days (34.2% versus 30.7%, p = .03).[127] The authors also noted that there was no increase in renal replacement therapy associated with colloid use.

Colloids—General
Colloids are more effective than crystalloids for expanding the plasma volume because they contain large, poorly diffusible solute molecules that create an osmotic pressure to keep water in the vascular space.[128] Animal models have shown that retention of a synthetic colloid (Voluven) in the intravascular space resulted in less extravasation of fluid into the lung than LR with a resulting improvement in oxygenation.[129]

Colloids include both human albumin solution and synthetic colloids. The most commonly used synthetic colloid is HES. There are significant variations in the composition and properties of HESs. Hextend has a mean molecular weight of approximately 670,000Da (range 450,000 to 800,000Da) and a molar substitution of approximately 0.75 (an average of approximately 75 hydroxyethyl groups per 100 glucose units). The HES molecules in Hextend are formulated in a balanced

crystalloid solution. Other HES variants may have different mean molecular weights or varying ratios of hydroxyethyl group substitutions. The HES molecules may also be dissolved in different solutions.

A meta-analysis of 19 reports (1567 patients) studying the use of 6% HES solution in surgical patients found no increase in the incidence of postoperative death or acute kidney injury in patients who received HES.[130] The HES solutions in this study had a variety of molecular weights and molar substitutions. The other fluids used were an assortment of different colloids and crystalloids. A Cochrane Review concluded that neither HES nor dextran has been shown to improve survival in hypovolemic patients compared with crystalloids.[131]

A recent article by Zarychanski et al noted an association between HES administration, acute kidney injury, and increased mortality. This meta-analysis of 38 trials did not focus specifically on hemorrhagic shock; it also included patients with diagnostic descriptors such as sepsis, burns, "ICU patients," and "post-cardiac arrest" as well as trauma. Patients in some studies were described as "trauma" or "hypovolemia."[131] Neither of these two terms is synonymous with "hemorrhagic shock." Outcomes after resuscitation with HES in a heterogeneous patient population may not reflect the effects of HES in patients with hemorrhagic shock.

The Zarychanski et al. report included HESs of various concentrations, various molecular weights, and various molar substitution ratios. As they note, different types of starch solutions may have different physiologic effects.[101] Results after treatment with an assortment of HES options do not necessarily reflect the effects of any single solution. The total volume of HESs infused in all of the trials reviewed by Zarychanski et al. was not well captured, but some of the volumes noted were well in excess of that recommended for the prehospital treatment of hemorrhagic shock in battlefield trauma care.[13,14] The study done at Ryder Trauma center in Miami, FL, used Hextend at the volume recommended by the US military (a 500mL bolus followed by a second 500mL bolus if required) and found no increased incidence of acute kidney injury due to Hextend.[132]

Of note also is that the Zarychanski et al. report did not address other potential complications of crystalloid or colloid fluid resuscitation such as abdominal compartment syndrome, ARDS, and worsening of cerebral edema in TBI.[131] The increased extravascular distribution of crystalloids must be considered in selecting a prehospital resuscitation fluid; crystalloids have been shown to produce an increase in these complications,[28,53,81,133] as well as an increase in mortality.[25]

The detrimental effect of crystalloids on TBI has been observed in animal models. In a swine model of TBI and hemorrhagic shock (40% blood volume controlled hemorrhage), the animals were resuscitated with NS, Hextend, or FFP. The volumes of Hextend and FFP matched the shed blood volume; NS was administered at 3 times the shed blood volume. The outcome measure was brain lesion size. Plasma reduced the size of the brain lesion. Hextend did not reduce the size of the brain lesion but reduced the amount of edema associated with the lesion in comparison to that produced by NS resuscitation.[134] Cerebral edema is a major concern in casualties who sustain moderate to severe TBI in addition to hemorrhagic shock.

Another retrospective study examined HES use in 2225 trauma patients; 497 patients (22%) received 6% HES (450/0.7) within 24 hours of admission to the hospital. (Note that Hextend has a different molecular weight and molar substitution [670/0.75] than 6% HES [450/0.7].) Acute kidney injury was defined as a rise in creatinine greater than 2 times baseline. ISS was greater in the HES group (29.7) compared with the no-HES group (27.5). Patients who died within 24 hours of admission were excluded. This is a significant limitation of the study because individuals who die from hemorrhagic shock often do so within the first 24 hours and exclusion of these patients introduces the potential for a survival bias. The mortality was 21% in the HES group and 11% in the no-HES group. The incidence of acute kidney injury was 13% in the HES group and 8 % in the no-HES group. The mean infused volume of HES was 725mL. Other options for fluid resuscitation included RBCs and plasma; the report notes that "there were no resuscitation protocols in place during the study period." The conclusion from this study was: "Because of the detrimental association with renal function and mortality, hetastarch should be avoided in the resuscitation of trauma patients." The study also notes that: "It has been argued that damage control resuscitation of a massively bleeding patient with plasma and blood may be beneficial. In this regard, abandoning synthetic colloids in favor of plasma may be appropriate."[135] Since this fluid resuscitation was carried out in the hospital where blood products were available, both TCCC and the Joint Trauma System Clinical Practice Guidelines would recommend that damage control resuscitation be accomplished with 1:1:1 plasma, PRBCs, and platelets. Crystalloids and colloids are clearly not the preferred fluid for resuscitation from hemorrhagic shock when blood components are available.[13,49]

The FDA issued a safety communication on HESs (Hespan, Hextend, and Voluven) in November 2013. The

warning noted an increased risk in mortality and renal replacement therapy associated with the use of these products as used to treat critically ill patients.[136] This communication did not mention the use of these products in the prehospital resuscitation of trauma patients, nor did it address the known increase in mortality and fluid overload complications resulting from the alternative use of large volume crystalloids in such patients.[6,25,28,53,61,81]

Hextend (HES 670/0.75 in a balanced electrolyte solution)

Hextend is the current CoTCCC-recommended resuscitation fluid when blood products are not available. Hextend remains in the intravascular space for a much longer period of time than do crystalloid solutions, thus providing a more sustained resuscitation with less volume of fluid and reducing the iatrogenic resuscitation injury caused by crystalloid-related edema. A study of patients requiring volume replacement during major surgery showed that Hextend (at an average dose of 1596mL) was as effective as 6% HES (670/0.7) in saline (Hespan) and resulted in less blood loss during surgery. In contrast to Hespan, Hextend did not significantly prolong the time to onset of clot formation (based on thromboelastography).[137]

No prospective trials in either the civilian or military sectors have studied the outcomes from hypotensive resuscitation with Hextend compared with other fluid resuscitation strategies. However, a US DoD performance improvement project studied the impact of prehospital fluid administration on outcomes in 530 combat casualties from Afghanistan in 2011 and 2012. Approximately two-thirds of the casualties had injuries sustained from blasts. The mean 2005 ISS was 22.4 for casualties who received Hextend (n = 65) and 17.9 for those who did not (n = 465.) Using the Shock Index (heart rate/SBP), 58.5% of Hextend patients were considered unstable (SI <0.5 or >0.9), while only 40% of non-Hextend patients were considered unstable. Although there was no statistically significant difference in mortality, a trend toward decreased mortality in the Hextend group was observed (1.5% versus 4.9%), despite the higher ISS and higher SI in the Hextend group. There were also no statistically significant differences in ARDS, increased intracranial pressure (ICP), compartment syndromes, mean creatinine values, or need for dialysis prior to discharge from the Level V medical treatment facility.[138]

The Hextend study by Ryan and colleagues performed at Ryder Trauma Center in Miami looked at all adults admitted during the study period who needed emergency surgery. This was a retrospective, nonrandomized study, since the community consent necessary to perform a randomized controlled trial in a prehospital setting is prohibited by Florida law. There were 281 blunt trauma patients and 209 patients with penetrating trauma. Patients received standard of care fluids as determined by the attending physician. Hextend was available on the formulary and used at the discretion of the responsible physician. The TCCC-recommended volume of Hextend (500mL initial volume followed by a second 500mL if clinically indicated) was used. The study did not examine subgroups with controlled and uncontrolled hemorrhage. While the study design limited its ability to determine a treatment benefit from Hextend use, the authors noted that there was no evidence of coagulopathy or renal injury when using the TCCC-recommended volume of Hextend.[132] In a discussion of these findings, Ogilvie noted that ". . . there is little doubt that Hextend did not promote coagulopathy when used for initial resuscitation, especially after penetrating trauma.[139]

The Martini et al. study discussed previously documented 100% survival 6 hours after an otherwise lethal 60% controlled hemorrhage model using volume-for-volume replacement of the blood lost with Hextend, but the volume-for-volume resuscitation strategy used did result in a dilutional coagulopathy.[43]

Voluven (HES 130/0.4 in NS)

Voluven is another synthetic HES solution that has a lower molecular weight and a smaller number of hydroxyethyl groups per molecule than Hextend. A study from South Africa compared Voluven to NS in a randomized, controlled, double-blinded study of 115 severely injured patients who received more than 3L of resuscitation fluid. No difference in mortality was found, but penetrating injury patients treated with Voluven were found to have less renal injury and better lactate clearance than those treated with NS. No differences were seen in patients who had sustained blunt trauma. Note that both fluids were given after arrival at the hospital.[140]

Myburgh et al.'s study examining the use of Voluven compared with NS in intensive care unit patients found no clinical benefit to Voluven and that Voluven patients had an increased rate of adverse events, including pruritus, skin rash, and renal replacement therapy.[141] Most of the patients in this study were sepsis rather than hemorrhagic shock patients. A study on the use of Voluven to replace blood lost during major surgery found that Voluven reduced clot strength and increased perioperative hemorrhage.[142] In contrast, a review on the use of HES solutions for volume replacement during surgery concluded that there were no indications that the use of tetrastarches (such as Voluven) results in adverse renal effects or increased blood loss during surgery.[143]

A prospective, randomized, controlled double-blind, multicenter trial with 100 patients compared Voluven to hetastarch (HES 670/0.75 in saline) for volume replacement during major orthopedic surgery and found that they were equally efficacious for this purpose. Voluven, however, had less effect on coagulation as measured by the nadir of factor VII and von Willebrand factor during the 2 hours post surgery.[144] It is important to note that this study used Voluven and HES in saline (Hespan) rather than Hextend.

Albumin
Albumin is a colloid derived from human plasma that has been used to resuscitate individuals in hemorrhagic and other types of shock. In a post-hoc analysis of 460 patients with TBI in the Saline versus Albumin Fluid Resuscitation (SAFE) study performed at 24 months after randomization, patients who had received albumin were found to have a higher mortality than those who had received saline (33.2% versus 20.4%). Among patients with severe brain injury, the increase in mortality was even larger (41.8% versus 22.2%).[145] This finding has resulted in the recommendation that albumin not be administered to trauma patients with TBI.[146,147] This restriction effectively precludes its use by combat medical personnel, since many of the casualties that they treat on the battlefield will have a combination of hemorrhagic shock and TBI. Several Cochrane reviews of albumin use for volume expansion in critically ill hypovolemic patients also noted that albumin did not confer a survival advantage over less expensive alternatives such as saline.[130,148]

Crystalloids—General
Crystalloids are electrolyte solutions whose main osmotically active particle is sodium. Sodium distributes throughout the extracellular fluid space. Since 75% to 80% of the extracellular fluid space is composed of interstitial fluid, that proportion of infused crystalloid is distributed into the interstitial space rather than remaining intravascular space. Crystalloids, therefore, have the predominant effect of expanding the interstitial space as opposed to the intravascular space.[127] An infused volume of 1L of 0.9% sodium chloride adds 275mL to the plasma volume and 825mL to the interstitial volume after equilibration. The total of these two volumes (1100mL) exceeds the infused volume because NS is slightly hypertonic and causes a small shift of fluid from the intracellular to the extracellular space.[127] Diffusion of crystalloids into the extravascular space may result in complications of resuscitation such as ARDS and hypoxemia,[12,19,81] as well as abdominal compartment syndrome.[28,53,133] A recent study of 799 patients who underwent trauma laparotomies found that reducing the volume of infused crystalloid reduced the incidence of ACS from 7.4% to 0% ($p = .001$).[28]

Beecher remarked in World War II that glucose and saline solutions were useful only in the treatment of dehydration.[22] Kwan noted in 2009: "Every year, tens of thousands of patients receive intravenous fluids for the management of bleeding. The Advanced Trauma Life Support (ATLS) protocol of the American College of Surgeons recommends the liberal use of isotonic crystalloid to correct hypotension in bleeding trauma patients. Nevertheless, we could find no reliable evidence to support or to not support this recommendation."[149] When crystalloids are used to replace blood loss, it is typical to infuse three times the volume of shed blood in order to replace the intravascular volume.[43,134,150] Animal studies have shown that crystalloid options designed to mitigate lactic acidosis have improved survival in hemorrhagic shock.[151]

Crystalloid-based resuscitation, but not blood products, is associated with increased risk of developing moderate-to-severe hypoxemia in trauma patients.[53] The authors of this study note that the negative effects of crystalloids in resuscitating trauma patients in hemorrhagic shock are becoming better understood. Another study states that: ". . . the disadvantages of crystalloids such as saline and lactated Ringer's solution for the management of hemorrhagic shock are well known."[56] Current DCR strategies include minimizing crystalloid for the resuscitation of patients with hemorrhagic shock to avoid potentiating the coagulopathy of trauma.[49,52,75]

Crystalloids—Lactated Ringer's
If blood products and Hextend are not available and a crystalloid fluid must be used, LR is preferred over NS because it does not produce the hyperchloremic acidosis that NS does.[152] In an animal model of controlled hemorrhage comparing LR, NS, Plasma-Lyte A, and Plasma-Lyte R, LR produced the highest 2-hour survival rate and was recommended by the authors as the best choice as a resuscitation fluid among the four crystalloids studied.[150] Waters et al. found that using LR for fluid replacement during abdominal aortic aneurysm repair produced less acidosis and less intraoperative blood loss than NS but with no decrease in mortality.[153]

Moore notes that the lack of a proven survival benefit from initial resuscitation with colloids as opposed to crystalloids, and the reduced expense of fluids like LR ($3 for 500mL of volume expansion) compared with albumin ($88 for albumin 5%) and Hextend ($17) argues in favor of using crystalloids like LR in US trauma centers.[154] A similar rationale was used by the IDF in deciding to use LR in their fluid resuscitation protocol, noting that their evacuation times are short and the cost difference was not justified.[155]

Crystalloids—Plasma-Lyte A

Plasma-Lyte A has a neutral pH (7.4), an osmolarity of 295mOsm/L, and no calcium, in contrast to LR, which has a lower pH, is slightly hypotonic (an osmolarity of 273mOsm/L), and contains calcium. The cost of Plasma-Lyte A from one vendor was $9.99 for a 1000mL bag,[156] but purchased in larger quantities, it is only minimally more expensive than LR.[96] Plasma-Lyte A was compared with NS in a study of 46 trauma patients and was associated with improved acid-base status and less hyperchloremia at 24 hours post-injury, although no improvement in survival was found in this small study.[157] This fluid is approved for use with blood and blood products, whereas LR is not recommended because the calcium in LR interacts with the components of RBC units and may cause the blood to coagulate.[157] At present, there is less published evidence with Plasma-Lyte A than with LR, but in an observational study of 30,994 patients who received NS during major surgery compared with 926 patients who received Plasma-Lyte A or Plasma-Lyte148, the patients who received Plasma-Lyte A had a lower incidence of postoperative infection, renal failure requiring dialysis, and the need for blood transfusion.[158]

Crystalloids—HTS

Volume resuscitation with HTS would seem to be an attractive option because the greater oncotic pressure of the hypertonic sodium solution allows for greater intravascular expansion than would occur with an equivalent volume of NS. A 250mL bolus of 7.5% sodium chloride solution increases the intravascular volume by approximately twice the infused amount. The additional volume comes from the extravascular and intracellular fluid spaces.[127] HTS also reduces the body's inflammatory response compared with infusion of isotonic crystalloids.[159]

The 1999 Institute of Medicine recommendations for treatment of shock were that (1) no fluids be provided to casualties whose hemorrhage is controlled and who are not in shock; (2) for casualties in shock from hemorrhage that has been controlled, 7.5% HTS be administered via the tibial intraosseous route as a 250mL bolus, to be followed by a second 250mL bolus if evacuation to definitive care is delayed; and (3) for casualties in shock from hemorrhage that has not been controlled, the treatment is the same as for controlled hemorrhage shock.[160] This recommendation has been echoed by others[161] but remains problematic in that 7.5% HTS is not approved by the FDA and therefore cannot be placed in the military logistics system.

Most of the human trials that have been conducted with HTS have used the non–FDA-approved 7.5% concentration.[159,162] HTS 10%is highly irritating to peripheral veins and even 7.5% HTS has been found to cause osteomyonecrosis when given intraosseously.[159] HTS 5%, which is FDA approved, also has the advantage of decreasing inflammatory response compared with standard crystalloid solutions and the ability to decrease ICP without causing hypotension.[159]

HTS has been shown to be effective as an initial resuscitation fluid,[163–165] but since HTS is a crystalloid, its effects when used alone (as opposed to being combined with a colloid) are short-lived.

Bulger and her coauthors performed a randomized controlled trial to examine the effects of 7.5% HTS compared with 7.5% HTS with dextran and compared with NS. The 853 study patients were all hypotensive from trauma (62% blunt; 38% penetrating). Study fluids were administered as a 250mL bolus by prehospital providers.[166] No difference in 28-day survival was found between the three study groups.

Dubose and his colleagues performed a prospective observational study of 51 trauma patients who received 500mL of 5% HTS with a matched cohort of trauma patients who did not receive HTS but were resuscitated with other crystalloids and blood products. HTS patients were observed to have elevated serum sodium for several days without any adverse effects associated with this elevation. There were no differences in coagulation parameters or mortality.[162]

HTS has been shown to both decrease cerebral edema and increase plasma volume in combined TBI and hemorrhagic shock.[167] A 2004 report in *JAMA* studied 229 TBI patients who were hypotensive and comatose and compared the effects of a 250mL bolus of either 7.5% HTS or LR in addition to conventional fluid resuscitation protocols used by paramedics. There was no effect on either survival to discharge or neurological function at 6-month follow-up.[168] Two points about this study are worthy of note: (1) it was again done with 7.5% HTS, which is not FDA approved and thus not available to combat medical providers; and (2) the patients in this study also received other crystalloid and colloid fluids in the prehospital phase of care, which make understanding the impact of the HTS versus the LR more difficult. HTS 3% has also been shown to be useful as an adjunct to improve primary fascial closure rates after damage control laparotomy.[169]

In a review of HTS for the USAISR Fluid Resuscitation Conference, Coimbra stated that, due to the paucity of studies examining small-volume 3% and 5% HTS use in resuscitation from hemorrhagic shock, additional studies are needed before this option can be recommended.[170]

HTS is currently recommended in the TCCC guidelines to decrease intracranial pressure in casualties with severe TBI who have physical findings suggestive of impending cerebral herniation.[171]

Crystalloids—NS

"Resuscitation with NS results in hyperchloremic acidosis. This acidosis may be associated with systemic vasodilation, increased extravascular lung water, and coagulopathy. The traditional indications for using NS to resuscitate trauma patients including traumatic head injury, the need to transfuse blood, and renal failure are not supported by randomized prospective trials. Rapid infusion of LR for resuscitation of hemorrhagic shock results in increased lactate levels that are not associated with acidosis."[152]

NS is not an optimal choice for resuscitation from hemorrhagic shock because of both hemodilution of clotting factors and the propensity of NS to cause hyperchloremic acidosis.[172,173] Aggressive resuscitation with saline-based resuscitation strategies is associated with a number of adverse effects, including increased bleeding, ARDS, multiorgan failure, ACS, and increased mortality.[32,174] In an animal model of uncontrolled hemorrhage resuscitated with various crystalloids and colloids, NS produced more acidosis and secondary blood loss than the other fluid options and caused the authors to question the use of this fluid as a resuscitation choice in hemorrhagic shock.[30] As noted previously, in a large clinical study, patients who received NS had more complications, including renal failure, than patients who received Plasma-Lyte A.[158]

Prehospital Fluid Resuscitation: Adding It All Up

As with medications, selecting the right amount of resuscitation fluid to be administered as well as the right fluid is critical to optimizing outcomes.

Fluid resuscitation studies performed in a nontrauma patient population are not necessarily relevant to the resuscitation of trauma patients in hemorrhagic shock.

In uncontrolled hemorrhage, the resuscitation option of choice is whole blood or 1:1:1 plasma, RBC units, and platelets, given at whatever rate is necessary to maintain tissue perfusion until bleeding can be controlled.

Advanced capability evacuation platforms that administer 1:1 plasma and RBC units en route are associated with a higher survival rate in subsets of severely injured casualties than evacuation platforms that do not have the capability to use blood components for resuscitation. Blood products have not, however, been proved

to be the reason for the increased survival. Use of prehospital blood products is now in place in some civilian trauma systems[175,176] and in the Royal Caribbean Cruise Line system.[64]

Unlike crystalloid, plasma does not cause coagulopathy (and, in fact, is used to treat coagulopathy). Plasma does not promote cerebral edema and has not been associated with increased mortality, acute kidney injury, or hypoxia, as crystalloid resuscitation has. There is, however, at present no mechanism or authority for most conventional medics, corpsmen, or PJs to administer prehospital plasma to their casualties before the TACEVAC phase of care. No DP product is currently approved by the FDA.

There is no evidence for benefit from large volume crystalloid resuscitation in uncontrolled hemorrhage. There is Level B clinical evidence that this approach reduces survival.[6]

There is Level B evidence that restricting fluid resuscitation volume in patients with uncontrolled hemorrhage is beneficial.[6]

"Although the use of resuscitation fluids is one of the most common interventions in medicine, no currently available resuscitation fluid can be considered to be ideal."[177]

There is Level B evidence that Hextend used in the volume recommended by TCCC to supplement fluid resuscitation in trauma patients is safe and does not result in a coagulopathy.[139,178]

There are no definitive clinical trials to answer the question of how combat medics, corpsmen, and PJs should resuscitate their casualties in hemorrhagic shock if blood and plasma are not available, but Hextend has the advantage of providing a prolonged (6- to 8-hour) intravascular presence in the absence of ongoing hemorrhage. Crystalloid solutions rapidly redistribute through the entire extravascular space after infusion and so must be infused in three times the volumes of Hextend to provide an equivalent volume expansion for 6 hours.[43] This continues to be an important factor for combat medical personnel who have to carry resuscitation fluids for long distances.

There is animal evidence showing that Hextend achieves 100% survival for 6 hours in a controlled hemorrhage model (60% of estimated blood volume) using a volume-for-volume replacement of shed blood with Hextend. Crystalloid resuscitation also produced 100% survival, but required approximately three times the infused volume of Hextend.[43] Smaller volumes of Hextend

also produced good survival rates in a study that used a 180-minute observation period.[44]

There is animal evidence showing that fluid resuscitation with both Hextend and LR causes a dilutional coagulopathy. Animals resuscitated with Hextend, however, exhibited return of base excess and lactate levels to prehemorrhage levels by the end of 6 hours. The LR animals did not, indicating better tissue perfusion with Hextend resuscitation.[43]

Hextend use has been seen in a Joint Trauma Ssystem performance improvement review to produce survival equivalent to the group who did not receive Hextend, despite the fact that the casualties in the Hextend group were more severely injured.

Crystalloids have been shown in animal models to increase the edema associated with TBI lesions.[134]

Medby states that the lack of clinical evidence showing benefit from either crystalloids or colloids used in the prehospital resuscitation of trauma victims in hemorrhagic shock necessitates a search for alternative resuscitation fluids.[179)]

NS causes hyperchloremic acidosis and should not be used for fluid resuscitation in hemorrhagic shock.

Although Plasma-Lyte A has not been widely used in the US military, it may be as good as or better than LR.

Conclusions

1. The preferred fluids for resuscitation of casualties in hemorrhagic shock, in descending order of preference, are:
   – Whole blood
   – 1:1:1 plasma, RBCs, and platelets
   – 1:1 plasma and RBCs
   – Reconstituted DP, liquid plasma, or thawed plasma alone or RBCs alone
   – Hextend
   – LR or Plasma-Lyte A

Notes:
*Plasma is strongly preferred over Hextend.
*Plasma-Lyte A can be used with RBC transfusions.
*NS is not recommended for hemorrhagic shock, but may be indicated for dehydration.
*NS has in the past been used as an adjunct to transfusing PRBCs (spun from WB – no additive solution – hematocrit [Hct] 60–70), but the RBCs infused now are RBCs in additive solution (spin – remove PRP – add additive solution – final Hct 55 – much lower viscosity than true PRBCs). These are the RBCs being transfused in theater at present.

*HTS is not recommended as a resuscitation fluid, but is recommended to decrease ICP in casualties with severe TBI who have physical findings suggestive of impending cerebral herniation.

2. Blood products are becoming increasingly available in the prehospital setting and are the resuscitation fluids of choice when feasible. The DoD should use whole blood or plasma and RBCs (in a 1:1 ratio) as far-forward as feasible, including evacuation platforms and some selected TFC locations. Platelets should also be used should they become available in far-forward settings in the future.

3. Both fresh whole blood and apheresis platelets, as currently collected and screened in deployed medical treatment facilities, are not FDA compliant. Non–FDA-compliant platelets should be used only when FDA-compliant platelets are not available (as is currently the case in deployed MTFs). Non–FDA-compliant whole blood should be used only when treatment with FDA-compliant blood components is not producing the desired clinical effect and FDA-compliant whole blood is not available.

4. In order to administer blood components safely in the prehospital combat setting and to optimize the benefit obtained from their use, a command or theater-approved protocol that has been coordinated with the appropriate clinical and blood and banking facilities should be in place. All medical personnel who will be responsible for administering blood products in the prehospital combat setting should be trained in the approved protocol.

5. Hextend is less desirable than blood components for fluid resuscitation. When available for point-of-injury care, liquid (never-frozen) or thawed plasma, or reconstituted DP is preferred over both crystalloids and colloids. The French DP product is currently being used by selected Special Operations units under a treatment protocol. The DoD should continue its aggressive efforts to obtain an FDA-approved DP product so that the use of DP can expanded to all military medical personnel who may care for combat casualties at or near the point of injury.

6. The DoD and the FDA should move to establish a Military Use Panel with a charter to grant military-specific approval where appropriate for medications not labeled for trauma or other products not yet FDA approved, but which are documented to be safe and effective and are of special interest to the military for use in battlefield trauma care.

7. The volume of fluid used in the resuscitation of casualties in hemorrhagic shock is an important factor in determining outcomes and the optimal volume may vary based on the type of injuries present.

8. Large-volume crystalloid fluid resuscitation for patients in shock caused by penetrating torso trauma

has been shown to decrease patient survival compared with resuscitation with restricted volumes of crystalloid.

9. Larger volumes of infused crystalloids have also been associated with increased mortality in trauma patients in studies where the authors did not categorize patients by controlled versus uncontrolled hemorrhage.

10. The smaller required volume and sustained intravascular presence of Hextend as recommended by TCCC is important to combat medical personnel who treat casualties in austere environments where evacuation times may be prolonged. Hextend may also decrease complications of crystalloid resuscitation such as ARDS and ACS, but does not decrease the dilutional coagulopathy caused by crystalloid resuscitation.

11. When tactical and logistical constraints prevent the use of the recommended blood products, hypotensive resuscitation with Hextend as outlined in the current TCCC guidelines should continue to be used for the resuscitation of casualties in hemorrhagic shock.

12. The emerging evidence on hetastarch use and acute kidney injury has not documented a problem with Hextend use for the indication (hemorrhagic shock) and in the volumes recommended by TCCC.

PROPOSED CHANGE TO THE TCCC GUIDELINES

Current Wording

Tactical Field Care

7. Fluid resuscitation
   Assess for hemorrhagic shock; altered mental status (in the absence of head injury) and weak or absent peripheral pulses are the best field indicators of shock.
   a. If not in shock:
      – No IV fluids necessary
      – PO fluids permissible if conscious and can swallow
   b. If in shock:
      – Hextend, 500mL IV bolus
      – Repeat once after 30 minutes if still in shock.
      – No more than 1000mL of Hextend
   c. Continued efforts to resuscitate must be weighed against logistical and tactical considerations and the risk of incurring further casualties.
   d. If a casualty with an altered mental status due to suspected TBI has a weak or absent peripheral pulse, resuscitate as necessary to maintain a palpable radial pulse.

Tactical Evacuation Care

7. Fluid resuscitation

Reassess for hemorrhagic shock (altered mental status in the absence of brain injury and/or change in pulse character.) If BP monitoring is available, maintain target systolic BP 80–90mmHg.
a. If not in shock:
   – No IV fluids necessary.
   – PO fluids permissible if conscious and can swallow.
b. If in shock and blood products are not available:
   – Hextend 500mL IV bolus
   – Repeat after 30 minutes if still in shock.
   – Continue resuscitation with Hextend or crystalloid solution as needed to maintain target BP or clinical improvement.
c. If in shock and blood products are available under an approved command or theater protocol:
   – Resuscitate with 2 units of plasma followed by PRBCs in a 1:1 ratio. If blood component therapy is not available, transfuse fresh whole blood. Continue resuscitation as needed to maintain target BP or clinical improvement.
d. If a casualty with an altered mental status due to suspected TBI has a weak or absent peripheral pulse, resuscitate as necessary to maintain a palpable radial pulse. If BP monitoring is available, maintain target systolic BP of at least 90mmHg.

PROPOSED CHANGE

Tactical Field Care and TACEVAC Care

7. Fluid resuscitation
   a. The resuscitation fluids of choice for casualties in hemorrhagic shock, listed from most to least preferred, are: whole blood*; plasma, RBCs and platelets in 1:1:1 ratio*; plasma and RBCs in 1:1 ratio; plasma or RBCs alone; Hextend; and crystalloid (lactated Ringer's or Plasma-Lyte A).
   b. Assess for hemorrhagic shock (altered mental status in the absence of brain injury and/or weak or absent radial pulse).
      1. If not in shock:
         – No IV fluids are immediately necessary.
         – Fluids by mouth are permissible if the casualty is conscious and can swallow.
      2. If in shock and blood products are available under an approved command or theater blood product administration protocol:
         – Resuscitate with whole blood*, or, if not available
         – Plasma, RBCs, and platelets in a 1:1:1 ratio*, or, if not available
         – Plasma and RBCs in 1:1 ratio, or, if not available;
         – Reconstituted dried plasma, liquid plasma or thawed plasma alone or RBCs alone;

– Reassess the casualty after each unit. Continue resuscitation until a palpable radial pulse, improved mental status or systolic BP of 80–90mmHg is present.
3. If in shock and blood products are not available under an approved command or theater blood product administration protocol due to tactical or logistical constraints:
   – Resuscitate with Hextend, or if not available;
   – Lactated Ringer's or Plasma-Lyte A;
   – Reassess the casualty after each 500mL IV bolus;
   – Continue resuscitation until a palpable radial pulse, improved mental status, or systolic BP of 80–90mmHg is present.
   – Discontinue fluid administration when one or more of the above end points has been achieved.
4. If a casualty with an altered mental status due to suspected TBI has a weak or absent peripheral pulse, resuscitate as necessary to restore and maintain a normal radial pulse. If BP monitoring is available, maintain a target systolic BP of at least 90mmHg.
5. Reassess the casualty frequently to check for recurrence of shock. If shock recurs, recheck all external hemorrhage control measures to ensure that they are still effective and repeat the fluid resuscitation as outlined above.

*Neither whole blood nor apheresis platelets as these products are currently collected in theater are FDA compliant. Consequently, whole blood and 1:1:1 resuscitation using apheresis platelets should be used only if all of the FDA-compliant blood products needed to support 1:1:1 resuscitation are not available, or if 1:1:1 resuscitation is not producing the desired clinical effect."

Vote: This change was approved by the required two-thirds or greater majority of the voting members of the CoTCCC.

Level of evidence (AHA/ACC[180])

The levels of evidence used by the American College of Cardiology and the American Heart Association were described by Tricoci in 2009:

Level A: Evidence from multiple randomized trials or meta-analyses.
Level B: Evidence from a single randomized trial or nonrandomized studies.
Level C: Expert opinion, case studies, or standards of care.

Using this taxonomy, the levels of evidence for the following aspects of fluid resuscitation from hemorrhagic shock are provided below.

1. Early hypotensive resuscitation with crystalloid improves survival compared with larger-volume crystalloid resuscitation in hypotensive trauma patients with penetrating torso injuries – Level B
2. Early resuscitation with 250mL of 7.5% HTS or 7.5% HTS/dextran did not improve 28-day survival in comparison to NS – Level B
3. Resuscitation using a 1:1 ratio of plasma and PRBCs improves survival over higher ratios of PRBCs to plasma – Level B
4. Resuscitation with fresh whole blood improves survival in comparison to resuscitation with 1:1 plasma and PRBCs – Level B
5. Resuscitation with RBCs, plasma, and warm FWB (but not apheresis platelets) was found in one study to improve survival compared with treatment with RBCs, plasma, and apheresis platelets (but not FWB) – Level B
6. Transfusion of a ratio of >1:8 apheresis platelets to RBCs (compared with ratios with smaller volumes of platelets) is associated with improved survival at 24 hours and at 30 days in combat casualties requiring a MT within 24 hours of injury – Level B

Considerations for Further Research and Development

1. Conduct a retrospective study of combat casualty outcomes in the DoDTR as a function of the type and volume of prehospital fluids administered as well as the status of the casualty (shock versus no shock) and the nature of the hemorrhage (controlled versus uncontrolled).
2. Explore all options to make an FDA-approved dried plasma product available for all US military combat medical providers. This product should be able to be transfused to casualties of any blood type; should be able to withstand the temperatures encountered in military prehospital settings; should have a long shelf life, and should not be packaged in breakable containers.
3. Fund studies in the civilian sector to compare the survival benefit from prehospital fluid resuscitation with plasma alone compared with resuscitation with crystalloids or colloids as well as with 1:1 plasma and RBCs. Include a subgroup analysis of controlled versus uncontrolled hemorrhage patients. Also recommend including relevant surrogate outcomes (indices of coagulopathy, shock, platelet dysfunction, etc.) that could be more readily explored in smaller studies.
4. Fund research and development efforts designed to enhance the availability, safety, efficacy, and shelf life of whole blood and blood components in the far-forward combat environment.
5. Study methods for increasing the availability, safety, efficacy, and shelf life of cold stored plasma, platelets, and whole blood in the deployed combat environment.

6. Fund the development and fielding of a platelet-sparing leukoreduction filter for collecting whole blood for transfusion.

7. Explore pathogen reduction technologies that can be used with blood products to increase transfusion safety and reduce the screening burden currently needed to ensure freedom from transfusion-transmitted pathogens.

8. Although blood products are the preferred fluid resuscitation option for casualties in hemorrhagic shock, logistical constraints may require that Hextend, LR, or Plasma-Lyte A be used in the prehospital phase of battlefield trauma care. Research should be carried out to determine which of these three fluids produces the best outcomes for civilian patients in hemorrhagic shock in trauma systems where prehospital blood and plasma are not used.

9. Develop methodology, training, and equipment to improve the ability of far-forward medical personnel to transfuse whole blood where possible.

10. Explore ways to expand the use of liquid (never-frozen) plasma as a way to enhance the availability of 1:1 plasma:RBC resuscitation on TACEVAC flights without delaying the missions in order to thaw frozen plasma.

11. Develop rapid transition programs to accelerate the fielding of newly developed fluid resuscitation products and technology to combat units.

12. Fund the continued development and expedited fielding of technologies that enable prehospital combat medical personnel to better evaluate the need for and the adequacy of fluid resuscitation. Examples of candidate technologies include the tissue oxygen saturation monitor and the cardiovascular reserve index.

13. A longer-term research goal to improve survival in hemorrhagic shock is the identification of pharmacologic agents that reduce metabolic demand until oxygen delivery capacity can be reestablished for casualties in shock.[38]

14. Establish a Military Use Panel as a shared effort between the DoD and the FDA. One purpose of this panel would be to consider the approval of a military indication label for medications that are currently labeled for other indications, but have applicability for military use. Examples include oral transmucosal fentanyl citrate, ketamine, and tranexamic acid. A second purpose of the proposed DoD-FDA Military Use Panel would be to evaluate products that have been approved for use by NATO allies and have applications for the US military, but which have not been approved by the FDA for use in the United States. The French and German dried plasma products are examples of such items.

15. Develop blood-banking methods and technologies that will enable whole blood and apheresis platelets collected in deployed medical treatment facilities to achieve FDA compliance.

Acknowledgments

Disclaimers

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the US Department of the Army or the Department of Defense. This recommendation is intended to be a guideline only and is not a substitute for clinical judgment.

Disclosures

Dr Weiskopf, in 2012, was part of a group that reviewed all tetrastarches use in surgery, resulting in the Van Der Linden review that is cited. The project was funded by Fresenius-Kabi. Dr Schreiber is funded by the NIH and the DoD to study resuscitation of hemorrhagic shock. He directed the clinical hemostasis research program at Novo Nordisk A/S 2005-07, and now consults for various governmental agencies and corporate entities in the fields of transfusion and hemostasis. Dr Champion is the president/CEO of SimQuest, LLC.

Release

This document was reviewed by the Director of the Joint Trauma System and by the Public Affairs Office and the Operational Security Office at the US Army Institute of Surgical Research. It is approved for unlimited public release.

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CAPT (Ret) Butler was a Navy SEAL platoon commander before becoming a physician. He is an ophthalmologist and a Navy undersea medical officer with over 20 years' experience providing medical support to Special Operations Forces. Dr Butler has served as the command surgeon for the US Special Operations Command. He is currently the chair of the Department of Defense's Committee on TCCC and director of Prehospital Trauma Care at the Joint Trauma System.

COL (Ret) Holcomb is a trauma surgeon. He was the former commander of the US Army Institute of Surgical Research and was the Army Surgeon General's trauma consultant while on active duty. He is now the head of the Division of Acute Care Surgery and the director of the Center for Translational Injury Research at the University of Texas Health Science Center at Houston. He is also a member of the American College of Surgeons Committee on Trauma.

Dr Schreiber is chief of Trauma, Critical Care & Acute Care Surgery at Oregon Health & Science University. He is chief of Region X of the Committee on Trauma and a colonel in the US Army Reserve. He has been deployed three times including as the Joint Theater Trauma System Director and is a member of the American College of Surgeons Committee on Trauma.

COL Kotwal is a family medicine and aerospace medicine physician. He is a former command surgeon for the 75th Ranger Regiment and deputy command surgeon for the US Army Special Operations Command. Until recently, he was the director of trauma care delivery at the Joint Trauma System.

Col (Ret) Jenkins is a trauma surgeon. He is currently the director of trauma at the Mayo Clinic in Rochester, Minnesota.

During his time on active duty in the Air Force, he served as principal advisor to the Air Force Surgeon General on all surgery and trauma-related issues for first-strike deployable teams and was the first director of the Joint Trauma System. He is also the chairman of the Trauma and Injury Subcommittee of the Defense Health Board.

Dr Champion is a trauma surgeon. For 20 years he was the chief of trauma and surgical critical care at the largest teaching hospital in Washington, DC. He is also a professor of surgery and senior advisor in trauma at the Uniformed Services University of the Health Sciences. He is a senior scientific advisor for the Office of Naval Research and is the president/CEO of SimQuest, LLC.

SGM Bowling is a Special Forces 18D medic. He is presently the senior enlisted medical advisor for the US Army Special Operations Command. His previous assignment was senior medic for the Army Special Missions Unit.

LTC Cap is a hematology-oncology physician. He is currently assigned to the US Army Institute of Surgical Research, where his research interests include transfusion medicine, IV hemostatic agents, coagulation, and trauma. LTC Cap is an associate professor of medicine at Uniformed Services University and program director for the Clinical Research Fellowship Program at San Antonio Military Medical Center.

Lt Col Dubose is an Air Force trauma surgeon. He was previously an attending at the Air Force Center for Sustainment of Trauma and Readiness Skills at the R. Adams Cowley Shock Trauma Center in Baltimore and is currently in a vascular surgery fellowship at Memorial Hermann Hospital in Houston.

Col (Ret) Dorlac is a trauma surgeon. He is the chief of acute care surgery, Division of Trauma and Surgical Critical Care at the University of Cincinnati Medical Center. During his 26 years on active duty in the Air Force, he was the trauma consultant to the Air Force Surgeon General from 2008 to 2011, the director of the Air Force C-STARS training program at the University of Cincinnati Medical Center from 2007 to 2011 and the trauma medical director at Landstuhl Regional Medical Center from 2004 to 2007.

Col (Ret) Dorlac is an intensivist at the University of Cincinnati. During her time on active duty in the Air Force, she served as the critical care consultant to the USAF Surgeon General, as the medical director for critical care air transport for USAF-Europe, and as medical director of the intensive care unit at Landstuhl Regional Medical Center in Germany. She was instrumental in the creation and development of the USAF Acute Lung Rescue Team.

Dr McSwain is a trauma surgeon and the director of the Trauma Service at the Spirit of Charity Hospital, Tulane University. He is the medical director of the Prehospital Trauma Life Support program. He is a former member of the American College of Surgeons Committee on Trauma, the surgeon for the New Orleans Police Department, and the medical director of the New Orleans Jazz Festival.

CAPT Timby is a pulmonary/critical care physician. He is presently the Deputy Medical Officer of the Marine Corps. His previous assignments include serving as force surgeon, US Marine Corps Forces Command and II Marine Expeditionary Force (Forward) in Afghanistan. He has also had a prior tour as the command surgeon for the Navy Special Missions Unit

COL Blackbourne is a trauma surgeon at the San Antonio Military Medical Center. He was previously the commander of the US Army Institute of Surgical Research and the former head of the Army Trauma Training Center at the Ryder Trauma Center in Miami.

CAPT Stockinger is a Navy trauma surgeon currently assigned to the Joint Trauma System in San Antonio, TX. He has extensive operational medicine experience, including East Timor, Haiti, OIF, and OEF.

Dr Weiskopf is professor emeritus, Department of Anesthesia and Perioperative Care, University of California, San Francisco. He directed the clinical hemostasis research program at Novo Nordisk A/S 2005-07, and now consults for various governmental agencies and corporate entities in the fields of transfusion and hemostasis.

CDR Strandenes is an anesthesiologist and the senior medical officer for the Norwegian Naval Special Operations Commando. He has been a leader in the international Special Operations cooperative effort to make blood products more available in the far-forward combat environment.

COL Gross is a trauma surgeon with prior experience with the US Special Operations Command and combat-deployed forward surgical teams. He is currently the deployed director of the Joint Theater Trauma System and the trauma consultant to the Army Surgeon General.

Col Bailey is a trauma surgeon. He is currently the director of the Joint Trauma System. Col Bailey was previously the head of the Air Force Center for Sustainment of Trauma and Readiness Skills at St. Louis University Medical Center.